Hepatitis C Virus Infection and Rheumatic Diseases

The Impact of Direct-Acting Antiviral Agents

Patrice Cacoub, MD[a,b,c,d,*], Cloé Commarmond, MD[a,b,c,d], David Sadoun, MD, PhD[a,b,c,d], Anne Claire Desbois, MD[a,b,c,d]

KEYWORDS

• Hepatitis C (HCV) • Rheumatic disorders • Arthralgia • Arthritis • Vasculitis • Sicca syndrome • Direct-acting antiviral agents (DAA) • Treatment

KEY POINTS

- Hepatitis C virus infection is associated with many extrahepatic manifestations, including rheumatic disorders such as arthralgia, myalgia, cryoglobulinemia vasculitis, and sicca syndrome.
- The treatment of hepatitis C virus infection has long been based on interferon alfa, which was contraindicated in many autoimmune/inflammatory disorders.
- The emergence of new oral interferon-free combinations now offers an opportunity for patients infected with hepatitis C virus with extrahepatic manifestations, including autoimmune/inflammatory disorders, to be cured with a short treatment duration and a low risk of side effects.

Approximately 130 million to 170 million people are infected with hepatitis C virus (HCV) worldwide. The HCV induces severe morbidity and mortality mainly caused by liver complications (cirrhosis, hepatocellular carcinoma). Shortly after HCV discovery in the early 1990s, this chronic viral infection was recognized to induce many

Conflict of Interest: P. Cacoub has received consultancies, honoraria, advisory board, or speakers' fees from Abbvie, AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen, Merck Sharp and Dohme, Pfizer, Roche, Servier, and Vifor. A.C. Desbois has received speakers' fees from Gilead. C. Commarmond has no conflicts of interest. D. Saadoun has received speakers' fees from Gilead.

Financial support: None.

[a] Inflammation-Immunopathology-Biotherapy Department (DHU i2B), Sorbonne Universités, UPMC Université Paris 06, UMR 7211, Paris F-75005, France; [b] INSERM, UMR_S 959, Paris F-75013, France; [c] CNRS, FRE3632, Paris F-75005, France; [d] Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, AP-HP, 83 boulevard de l'hôpital, Paris F-75013, France

* Corresponding author. Department of Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, AP-HP, 83 boulevard de l'hôpital, Paris F-75013, France.

E-mail address: patrice.cacoub@aphp.fr

Rheum Dis Clin N Am ■ (2016) ■–■

http://dx.doi.org/10.1016/j.rdc.2016.09.011 **rheumatic.theclinics.com**

extrahepatic manifestations. Large studies have highlighted increased HCV-related morbidity and mortality caused by cryoglobulinemia vasculitis, B-cell non-Hodgkin lymphoma, arthralgia, myalgia, sicca syndrome, as well as cardiovascular diseases, type 2 diabetes and insulin resistance, and neurocognitive dysfunction.[1,2] Interferon alfa (IFN) has long been the cornerstone of antiviral combinations in patients infected with HCV with a low rate of efficacy and a poor tolerance. In addition, use of IFN was associated with high rates of severe adverse events. In patients infected by HCV and with autoimmune/inflammatory rheumatic diseases, IFN was either contraindicated or reported to induce a flare of the disease. Recently, new direct-acting antiviral (DAA) IFN-free treatments led to HCV cure in most (>90%) patients with a good safety profile (severe adverse events <5%) and a short duration (12 weeks). This article focuses on the main rheumatologic diseases associated with chronic HCV infection, and the impact of DAAs on such extrahepatic manifestations.

HEPATITIS C VIRUS AND JOINT MANIFESTATIONS

Arthralgia/Myalgia

Arthralgia is reported in 6% to 20% of patients infected with HCV.[3–5] It usually involves large joints, sometimes with effusion, and is bilateral and symmetric. Arthralgia most frequently involve fingers, knees, and back.[6] Arthralgia is significantly more frequent in patients with cryoglobulinemia vasculitis compared with those without vasculitis (28% vs 23% respectively).[3] The presentation may mimic a rheumatoid arthritis. The frequent positivity of a rheumatoid factor activity in patients infected with HCV also leads to misdiagnosis. Smoking and a previous diagnosis of arthritis are independent risk factors for self-reported joint pain (odds ratio [OR], 5 and 4.25, respectively). Myalgia is less common, affecting about 2% to 5% of patients with HCV.[3,5] Arthritis, unrelated to mixed cryoglobulinemia, is less common (<5% of patient), involving small joints associated with carpal tunnel syndrome and palmar tenosynovitis.

Hepatitis C Virus Mixed Cryoglobulinemia Vasculitis

Mixed cryoglobulinemia vasculitis (CryoVas) is an immune complex small vessel vasculitis involving mainly the skin, the joints, the peripheral nerve system, and the kidneys.[1,2] Cryoglobulinemia is defined by the presence of circulating immunoglobulins that precipitate at cold temperatures and dissolve with rewarming. CryoVas is related to HCV infection in 70% to 80% of cases, mostly associated with a type II immunoglobulin (Ig) M kappa mixed cryoglobulin. In contrast, 50% to 60% of patients infected with HCV produce a mixed cryoglobulin that leads to CryoVas in 15% of cases. Main symptoms include asthenia, purpura, arthralgia, myalgia, peripheral neuropathy, and glomerulonephritis.[7,8] In a large cohort of patients with HCV-CryoVas, baseline factors associated with a poor prognosis were the presence of severe liver fibrosis (hazard ratio [HR], 5.31), central nervous system involvement (HR, 2.74), kidney involvement (HR, 1.91), and heart involvement (HR, 4.2).[9] Arthralgia is reported in 40% to 80% of patients infected with HCV and positive for a mixed cryoglobulin.[10–12] Joint pains are bilateral, symmetric, nondeforming, and involve mainly knees and hands, less commonly elbows and ankles. Rheumatoid factor (RF) activity is found in 70% to 80% of patients with CryoVas, not correlated with the occurrence of joint disease. Anti–cyclic citrullinated peptide (anti-CCP) antibodies are usually absent in patients with HCV. Clinically or on imaging, there is no evidence of joint destruction. Of note, some clinical features might be confusing for clinicians, because IFN treatment used for HCV may lead to exacerbation of arthralgia and myalgia. Sometimes it used to be difficult to distinguish vasculitis flares and side effects of IFN-based treatments.

Sicca Syndrome

Sicca symptoms of either the mouth or eyes have been reported in 10% to 30% of patients infected with HCV. Less than 5% of patients with a defined Sjögren syndrome are HCV positive.[10] In a recent literature review, Younossi and colleagues[13] reported a sicca syndrome prevalence of 11.9% in patients with HCV, with a risk ratio for sicca syndrome of 2.29 in patients infected with HCV compared with uninfected patients. However, the criteria for Sjögren syndrome diagnosis were based on clinical questionnaire in some studies and were not well detailed. Although sicca symptoms are very common in patients infected with HCV, a characterized Sjögren syndrome defined by the presence of anti-SSA or anti-SSB antibodies and a typical salivary gland histology is uncommon. A large cohort study of 137 patients with a definite Sjögren syndrome (1993 international criteria) compared patients with HCV infection with those with a primary form. Patients with HCV-associated Sjögren syndrome were older; more frequently male; and more frequently presented a vasculitis, a peripheral neuropathy, and a neoplasia. They also had a different biological pattern; that is, they more frequently had a positive RF test, a cryoglobulinemia, and less frequently anti-SSA or SSB antibodies.[14,15] Only 23% of patients with HCV-associated Sjögren syndrome had positive anti-extractable nuclear antigen. The detection of HCV RNA and HCV core antigen in epithelial cells of patients with HCV-associated Sjögren syndrome and the development of Sjögren syndrome–like exocrinopathy in transgenic mice carrying the HCV envelope genes support the possibility of a direct impact of HCV on the development of sialadenitis.[16,17]

Fibromyalgia and Fatigue

In a large prospective study, 19% of 1614 patients infected with HCV fulfilled the main diagnostic criteria of fibromyalgia (fatigue, arthralgia, and myalgia).[3] Fatigue, with or without a fibromyalgia, was the most frequent extrahepatic manifestation (35%–67%). Many underlying factors were independently associated with fatigue, such as older age, female gender, the presence of arthralgia/myalgia, as well as neuropsychological factors. In contrast, there was no link with alcohol consumption, HCV genotype or viral load, the presence of a cryoglobulin, and thyroid dysfunction. Of note, after IFN-based treatment, only the group of patients with a sustained virologic response showed a beneficial impact on fatigue. A benefit of treatment on arthralgia/myalgia was found in about 50% of patients, independently of the virologic response.

Production of Autoantibodies

The prevalence of circulating autoantibodies is high in patients with chronic HCV infection, which may cause diagnostic difficulties in patients with rheumatic manifestations.[3,10] The most frequent immunologic abnormalities include mixed cryoglobulins (50%–60%); RF activity (40%); and antinuclear (20%–35%), anticardiolipin (10%–15%), antithyroid (10%), and anti–smooth muscle antibodies (7%).[3,18,19] At least 1 immunologic abnormality is present in up to 53% of patients infected with HCV. The presence of such antibodies (ie, RF, antinuclear, or anticardiolipin) is usually not associated with specific clinical symptoms related to autoimmune disease.[3,20] The most frequent risk factors for the presence of such biological extrahepatic manifestations are the presence of extensive liver fibrosis and older age.[3,19]

Underlying Mechanisms

There are multiple immunologic factors predisposing patients infected with HCV to develop a CryoVas or other systemic rheumatologic manifestations. Chronic

stimulation of B cells by HCV directly modulates B-cell and T-cell function and results in polyclonal activation and expansion of B cell–producing IgM with RF activity. There is an expansion of clonal $CD21^{-/low}IgM^{+}CD27^{+}$ marginal zone–like B cells,[21] and a decrease of regulatory T cells.[22] In a genome-wide association study, significant associations were identified on chromosome 6.[23] A higher percentage of a particular allele of the promoter of the B cell–activating factor has been shown.[24] In contrast, specific virologic factors (viral load, genotype) have not been identified. Other factors are related to the infection by HCV of peripheral blood mononuclear cells, including peripheral dendritic cells, monocytes, and macrophages.[25] A persistent viral stimulation enhances expression of lymphomagenesis-related genes, particularly the activation-induced cytidine deaminase, which is critical for somatic hypermutation and could lead to polyclonal and, later, monoclonal expansion of B cells.[26] Under this trigger effect, oligoclonal or monoclonal IgM, which share rheumatoid activity, are produced by a permanent clone of B cells that favors the appearance of immune complexes, formed by circulating HCV, anti-HCV polyclonal IgG, and the monoclonal IgM.

IMPACT OF HEPATITIS C VIRUS CHRONIC INFECTION IN PATIENTS WITH RHEUMATOLOGIC DISORDERS

Increased Cardiometabolic-related Morbidity and Mortality

Many chronic autoimmune rheumatic diseases are now well recognized as independent risk factors for major cardiovascular events. Recent data also provide evidence of a strong relationship between HCV infection and major adverse cardiovascular events. Such risk has been shown to be higher in patients infected with HCV compared with controls without HCV, independently of the severity of the liver disease or the common cardiovascular risk factors. Patients with HCV chronic infection have an increased prevalence of carotid atherosclerosis and increased intima-media thickness compared with healthy controls or patients with hepatitis B or nonalcoholic steatohepatitis. Active chronic HCV infection seems to be an independent risk factor for ischemic cerebrovascular accidents and ischemic heart disease.[27] For example, Maruyama and colleagues[28] reported an improvement in the myocardial perfusion defect in patients who were cured from HCV infection after IFN-based treatment, whereas relapsers showed worsening. Successful IFN-based therapy showed a beneficial impact on the cardiovascular risk, underlining the tight link between HCV and the occurrence of cardiovascular events.[29–31] Consistently, HCV infection has been associated with higher rates of diabetes mellitus and insulin resistance compared with healthy volunteers and patients with hepatitis B. In addition, glucose abnormalities in patients with HCV are associated with poor liver outcomes, defined by advanced liver fibrosis, lack of sustained virologic response to IFN-based treatment, and a higher risk of hepatocellular carcinoma development.[32–35] In the context of chronic inflammatory rheumatologic disorders, which already lead to an increased cardiovascular risk (related to chronic inflammation), the presence of HCV infection should be taken into account to assess the global cardiovascular risk.

Rheumatologic Impact

Studies analyzing the impact of HCV infection on the prognosis of patients with chronic inflammatory rheumatologic disorders are scarce. In a recent prospective cohort of US veterans, HCV-positive patients reported higher pain scores, had higher tender joint counts, and higher patient global scores contributing to higher disease activity score (DAS)28 scores, after adjustment for age, gender, race, smoking status,

and days from enrollment.[36] After further adjustments for differences in the use of methotrexate, prednisone, and anti-TNF therapies, DAS28 scores remained significantly higher in HCV-positive patients over all study visits. There was no difference in physician-reported outcomes (swollen joints or physician global scores). After adjusting for age, gender, and race, HCV-positive patients were more likely to use prednisone (OR, 1.41) and anti-TNF therapies (OR, 1.51), and far less likely to use methotrexate (OR, 0.27).[36]

TREATMENT OF HEPATITIS C VIRUS INFECTION

Before the Era of Direct-acting Antiviral Combinations

The cornerstone of HCV-CryoVas therapy is the capacity of treatments to achieve a sustained virologic response. Introduced in the early 1980s as a monotherapy, IFN was found to be both poorly tolerated and poorly effective with virologic cure (sustained virologic response [SVR]) in less than 10%. With pegylated formulations of IFN (Peg-IFN) optimizing its pharmacokinetics and combination with ribavirin for 48 weeks or longer, SVR rates increased to about 50%. During the decade 2000 to 2010, Mazzaro and colleagues[37] first reported sustained clinical and virologic response in 44% of patients with HCV-CryoVas treated with Peg-IFN plus ribavirin for 12 months. Saadoun and colleagues[38] reported that the combination of Peg-IFN plus ribavirin compared with IFN plus ribavirin showed higher rates of complete clinical (67.5% vs 56.2%) and virologic (62.5% vs 53.1%) responses, regardless of HCV genotype and viral load. An early virologic response was associated with a complete clinical response (OR, 3.53; 95% confidence interval [CI], 1.18, 10.59), whereas a glomerular filtration rate less than 70 mL/min was a negative predictor (OR, 0.18; 95% CI, 0.05, 0.67). However, the safety profile was not satisfactory and such therapies often led to many severe adverse events, such as severe cytopenia, disabling fatigue, fever, and depression. In addition, fatigue, arthralgia, and myalgia were frequently reported, which is a particular concern in rheumatology patients in whom distinguishing drug side effect from underlying disease was often difficult.[39] Although nonspecific arthralgia has been reported, some investigators have published rare cases of rheumatoid arthritis occurrence with anti-CCP antibodies after IFN-based treatment despite HCV cure.[40,41] Consistently, other autoimmune exacerbations, such as Sjögren syndrome and systemic lupus erythematosus, have been reported after IFN treatments.[42] In the context of CryoVas, it has been reported cases of peripheral neuropathy induced or flared by IFN-based treatment.[43]

THE ERA OF DIRECT-ACTING ANTIVIRAL COMBINATIONS

The beginning of the new era was characterized by the development of the first 2 DAA agents: boceprevir and telaprevir. In combination with Peg-IFN and ribavirin, these first-generation HCV protease inhibitors significantly improved the efficacy of antiviral combination, leading to approximately 70% SVR rate in genotype 1 HCV infection. However, these agents worsened the toxicity of IFN-based treatments, which limited their use in all patients with HCV as well as in patients with rheumatic diseases.[15] In a prospective cohort of patients with HCV treated with boceprevir, the SVR rate was lower in cryoglobulinemic patients than in those without mixed cryoglobulinemia (23.8% vs 70% respectively; $P = .01$),[44] although the latter had more risk factors of treatment failure (severe liver fibrosis). The boceprevir-based treatment allowed improvement of symptoms on undetectable viremia and resulted in cryocrit disappearance in 86% of patients. However, symptoms reappeared after virologic breakthrough.[44] In another prospective study, telaprevir or boceprevir showed complete

clinical response and SVR at week 24 in 67% of patients. However, serious adverse events occurred in 46.6% of patients, mostly in patients with baseline severe liver fibrosis and a low platelet count.[44,45]

More recently, new all-oral, IFN-free, as well as ribavirin-free regimens have been approved. They are characterized by a dramatic efficacy leading to cure rates of 90% to 100% in all HCV genotypes, with minimal side effects and short duration (12–24 weeks).[46,47] Even in difficult-to-treat populations, including cirrhotic and previously treated patients, IFN-free DAA regimens have been reported to be very efficient. Numerous large prospective studies have been published with different DAA combinations, such as simeprevir plus sofosbuvir,[48] sofosbuvir plus daclatasvir with/without ribavirin, or sofosbuvir plus ledipasvir, showing high antiviral potency (>90% SVR rates in both cirrhotic and treatment-experienced patients whatever the stage of fibrosis).[49] Although such treatments remain expensive, they now offer a therapeutic revolution for patients infected with HCV, particularly those with rheumatic diseases in whom IFN-based treatment has failed or was not well tolerated.

For the treatment of HCV-CryoVas, the VASCUVALDIC study enrolled 24 patients (median age, 56.5 years; 54% male; 50% cirrhotic) who received sofosbuvir plus ribavirin for 24 weeks.[12] Seven patients also received immunosuppressive therapy: that is, rituximab, corticosteroids, and plasmapheresis. Eighty-seven percent of patients were complete clinical responders and SVR was obtained in 74% of patients at week12 posttreatment. Of note, the complete clinical response was very rapid because it was noted at on-treatment week 12 in two-thirds of patients. Kidney involvement with membranoproliferative glomerulonephritis improved in 4 out of 5 patients. Only 2 (8%) serious adverse events were observed. Sise and colleagues[50] reported a retrospective case series of 12 patients with HCV-CryoVas (median age, 61 years; 58% male; 50% cirrhotic) treated with sofosbuvir plus simeprevir (n = 8) or sofosbuvir plus ribavirin (n = 4). Seven patients had evidence of renal involvement, including 5 patients with membranoproliferative glomerulonephritis. Four patients received rituximab concurrent with DAA therapy. An SVR at posttreatment week 12 was achieved in 83% of patients. Cryoglobulin levels decreased in most patients, with a median decrease from 1.5% to 0.5%, and disappeared in 4 out of 9 cases. Only 2 (17%) patients experienced serious adverse events. The Italian experience was recently reported in 37 patients with HCV-CryoVas who received DAAs.[51] Ten percent of patients also received immunosuppressants. A response on CryoVas symptoms was defined as complete in 18 (49%) and partial in 13 (35%), whereas no response was noted in 6 (16%) patients.

Despite the unquestionable evidence of a viral cause and the obvious efficacy of antiviral treatments, immunosuppression remains a major treatment in patients with HCV-CryoVas in cases of severe presentation (renal, digestive, or cardiac involvements) or in patients with failure or contraindication to antiviral treatment. Rituximab (a monoclonal anti–CD20 antibody) targets activated B cells, which are responsible for cryoglobulin production and eventually CryoVas lesions. Randomized controlled trials showed that rituximab has a better efficacy than conventional immunosuppressive treatments (ie, glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis) or placebo.[52,53] Two other controlled trials showed that addition of rituximab to Peg-IFN/ribavirin led to a shorter time to clinical remission, better renal response rate, and higher rates of cryoglobulin clearance.[54,55] Of note, paradoxic worsening of vasculitis has also been described after rituximab in such patients. Rituximab may form a complex with IgMk mixed cryoglobulin and lead to severe exacerbation of vasculitis involvements.[56] Considering the very rapid and potent virologic efficacy of new DAA combination and the proven correlation between SVR and clinical

response, the exact place of rituximab, plasmapheresis, or other immunosuppressive drugs remains to be defined.[56] Other treatments for CryoVas have a limited place. Corticosteroids, used alone or in addition to IFN, did not favorably affect the response of HCV-CryoVas manifestations in controlled studies.[57] Plasmapheresis, which offers the advantage of removing the pathogenic cryoglobulins from the circulation, should be considered for rapidly progressive glomerulonephritis or life-threatening involvements. Immunosuppressive therapy is usually needed in association with plasma exchange in order to avoid the rebound increase in cryoglobulin serum level seen after discontinuation of apheresis. When used in combination with HCV treatment, plasmapheresis did not modify the virologic response if IFN was given after each plasma exchange session.[58] There are no available data to date with DAA.

The impact of new DAAs on other rheumatologic manifestations (ie, arthralgia, myalgia, and sicca syndrome) is unknown. For fibromyalgia, Younossi and colleagues[59] recently reported major benefits of sofosbuvir-based DAAs on most patient-reported outcomes, including mental and physical fatigue, at week 12 and week 24 posttreatment. A benefit of DAAs was also suggested on cerebral magnetic resonance signal in basal ganglia correlated with the virologic response.[60]

In conclusion, HCV chronic infection, apart from its liver-related complications, is frequently associated with clinical and biological rheumatologic manifestations, such as arthralgia, myalgia, cryoglobulinemia vasculitis, sicca syndrome, and the production of autoantibodies. Treatment of HCV has long been based on IFN, excluding most patients with rheumatisms because of the poor efficacy, high rates of side effects, and the risk of exacerbation of autoimmune and rheumatic disorders. The emergence of new oral IFN-free combinations now offers the opportunity for patients infected with HCV with extrahepatic manifestations such as rheumatic disorders to be cured with a low risk of side effects and a short treatment duration.

REFERENCES

1. Cacoub P, Gragnani L, Comarmond C, et al. Extrahepatic manifestations of chronic hepatitis C virus infection. Dig Liver Dis 2014;46(Suppl 5):S165–73.
2. Ferri C, Sebastiani M, Giuggioli D, et al. Hepatitis C virus syndrome: a constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer. World J Hepatol 2015;7:327–43.
3. Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis Rheum 1999;42:2204–12.
4. Cheng Z, Zhou B, Shi X, et al. Extrahepatic manifestations of chronic hepatitis C virus infection: 297 cases from a tertiary medical center in Beijing, China. Chin Med J (Engl) 2014;127:1206–10.
5. Mohammed RHA, ElMakhzangy HI, Gamal A, et al. Prevalence of rheumatologic manifestations of chronic hepatitis C virus infection among Egyptians. Clin Rheumatol 2010;29:1373–80.
6. Ogdie A, Pang WG, Forde KA, et al. Prevalence and risk factors for patient-reported joint pain among patients with HIV/hepatitis C coinfection, hepatitis C monoinfection, and HIV monoinfection. BMC Musculoskelet Disord 2015;16:93.
7. Landau D-A, Scerra S, Sene D, et al. Causes and predictive factors of mortality in a cohort of patients with hepatitis C virus-related cryoglobulinemic vasculitis treated with antiviral therapy. J Rheumatol 2010;37:615–21.

8. Ferri C, Sebastiani M, Giuggioli D, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. Semin Arthritis Rheum 2004;33:355–74.
9. Terrier B, Semoun O, Saadoun D, et al. Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis. Arthritis Rheum 2011;63:1748–57.
10. Cacoub P, Renou C, Rosenthal E, et al. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Medecine Interne et Maladies Infectieuses sur le Virus de l'Hepatite C. Medicine (Baltimore) 2000;79:47–56.
11. Lee YH, Ji JD, Yeon JE, et al. Cryoglobulinaemia and rheumatic manifestations in patients with hepatitis C virus infection. Ann Rheum Dis 1998;57:728–31.
12. Saadoun D, Thibault V, Si Ahmed SN, et al. Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVALDIC study. Ann Rheum Dis 2016;75(10):1777–82.
13. Younossi Z, Park H, Henry L, et al. Extra-hepatic manifestations of hepatitis C—a meta-analysis of prevalence, quality of life, and economic burden. Gastroenterology 2016;150(7):1599–608.
14. Brito-Zerón P, Gheitasi H, Retamozo S, et al. How hepatitis C virus modifies the immunological profile of Sjögren syndrome: analysis of 783 patients. Arthritis Res Ther 2015;17:250.
15. Ramos-Casals M, Loustaud-Ratti V, De Vita S, et al. Sjögren syndrome associated with hepatitis C virus: a multicenter analysis of 137 cases. Medicine (Baltimore) 2005;84:81–9.
16. Arrieta JJ, Rodríguez-Iñigo E, Ortiz-Movilla N, et al. In situ detection of hepatitis C virus RNA in salivary glands. Am J Pathol 2001;158:259–64.
17. Koike K, Moriya K, Ishibashi K, et al. Sialadenitis histologically resembling Sjogren syndrome in mice transgenic for hepatitis C virus envelope genes. Proc Natl Acad Sci U S A 1997;94:233–6.
18. Khairy M, El-Raziky M, El-Akel W, et al. Serum autoantibodies positivity prevalence in patients with chronic HCV and impact on pegylated interferon and ribavirin treatment response. Liver Int 2013;33:1504–9.
19. Hsieh M-Y, Dai C-Y, Lee L-P, et al. Antinuclear antibody is associated with a more advanced fibrosis and lower RNA levels of hepatitis C virus in patients with chronic hepatitis C. J Clin Pathol 2008;61:333–7.
20. Himoto T, Masaki T. Extrahepatic manifestations and autoantibodies in patients with hepatitis C virus infection. Clin Dev Immunol 2012;2012:871401.
21. Terrier B, Joly F, Vazquez T, et al. Expansion of functionally anergic CD21-/low marginal zone-like B cell clones in hepatitis C virus infection-related autoimmunity. J Immunol 2011;187:6550–63.
22. Saadoun D, Rosenzwajg M, Joly F, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. N Engl J Med 2011;365:2067–77.
23. Zignego AL, Wojcik GL, Cacoub P, et al. Genome-wide association study of hepatitis C virus- and cryoglobulin-related vasculitis. Genes Immun 2014;15:500–5.
24. Gragnani L, Piluso A, Giannini C, et al. Genetic determinants in hepatitis C virus-associated mixed cryoglobulinemia: role of polymorphic variants of BAFF promoter and Fcγ receptors. Arthritis Rheum 2011;63:1446–51.
25. Caussin-Schwemling C, Schmitt C, Stoll-Keller F. Study of the infection of human blood derived monocyte/macrophages with hepatitis C virus in vitro. J Med Virol 2001;65:14–22.

26. Muramatsu M, Kinoshita K, Fagarasan S, et al. Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme. Cell 2000;102:553–63.
27. Domont F, Cacoub P. Chronic hepatitis C virus infection, a new cardiovascular risk factor? Liver Int 2016;36:621–7.
28. Maruyama S, Koda M, Oyake N, et al. Myocardial injury in patients with chronic hepatitis C infection. J Hepatol 2013;58:11–5.
29. Hsu Y-H, Hung P-H, Muo C-H, et al. Interferon-based treatment of hepatitis C virus infection reduces all-cause mortality in patients with end-stage renal disease: an 8-year nationwide cohort study in Taiwan. Medicine (Baltimore) 2015;94: e2113.
30. Hsu Y-C, Lin J-T, Ho HJ, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. Hepatology 2014;59:1293–302.
31. Hsu C-S, Kao J-H, Chao Y-C, et al. Interferon-based therapy reduces risk of stroke in chronic hepatitis C patients: a population-based cohort study in Taiwan. Aliment Pharmacol Ther 2013;38:415–23.
32. Elkrief L, Chouinard P, Bendersky N, et al. Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. Hepatology 2014;60:823–31.
33. Huang Y-W, Yang S-S, Fu S-C, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis C patients with new-onset diabetes: A nationwide cohort study. Hepatology 2014;60:807–14.
34. Hung C-H, Lee C-M, Wang J-H, et al. Impact of diabetes mellitus on incidence of hepatocellular carcinoma in chronic hepatitis C patients treated with interferon-based antiviral therapy. Int J Cancer 2011;128:2344–52.
35. Eslam M, Aparcero R, Kawaguchi T, et al. Meta-analysis: insulin resistance and sustained virological response in hepatitis C. Aliment Pharmacol Ther 2011;34: 297–305.
36. Patel R, Mikuls TR, Richards JS, et al. Disease characteristics and treatment patterns in veterans with rheumatoid arthritis and concomitant hepatitis C infection. Arthritis Care Res 2015;67:467–74.
37. Mazzaro C, Zorat F, Caizzi M, et al. Treatment with peg-interferon alfa-2b and ribavirin of hepatitis C virus-associated mixed cryoglobulinemia: a pilot study. J Hepatol 2005;42:632–8.
38. Saadoun D, Resche-Rigon M, Thibault V, et al. Antiviral therapy for hepatitis C virus–associated mixed cryoglobulinemia vasculitis: a long-term followup study. Arthritis Rheum 2006;54:3696–706.
39. Cacoub P, Comarmond C, Domont F, et al. Cryoglobulinemia vasculitis. Am J Med 2015;128:950–5.
40. Yang D, Arkfeld D, Fong T-L. Development of anti-CCP-positive rheumatoid arthritis following pegylated interferon-α2a treatment for chronic hepatitis C infection. J Rheumatol 2010;37:1777.
41. Cacopardo B, Benanti F, Pinzone MR, et al. Rheumatoid arthritis following PEG-interferon-alfa-2a plus ribavirin treatment for chronic hepatitis C: a case report and review of the literature. BMC Res Notes 2013;6:437.
42. Onishi S, Nagashima T, Kimura H, et al. Systemic lupus erythematosus and Sjögren's syndrome induced in a case by interferon-alpha used for the treatment of hepatitis C. Lupus 2010;19:753–5.
43. Stübgen J-P. Interferon alpha and neuromuscular disorders. J Neuroimmunol 2009;207:3–17.

44. Gragnani L, Fabbrizzi A, Triboli E, et al. Triple antiviral therapy in hepatitis C virus infection with or without mixed cryoglobulinaemia: A prospective, controlled pilot study. Dig Liver Dis 2014;46:833–7.
45. Saadoun D, Resche Rigon M, Pol S, et al. PegIFNα/ribavirin/protease inhibitor combination in severe hepatitis C virus-associated mixed cryoglobulinemia vasculitis. J Hepatol 2015;62:24–30.
46. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889–98.
47. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014; 370:211–21.
48. Sulkowski MS, Vargas HE, Di Bisceglie AM, et al. Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection. Gastroenterology 2016;150:419–29.
49. Pol S, Corouge M, Vallet-Pichard A. Daclatasvir-sofosbuvir combination therapy with or without ribavirin for hepatitis C virus infection: from the clinical trials to real life. Hepat Med 2016;8:21–6.
50. Sise ME, Bloom AK, Wisocky J, et al. Treatment of hepatitis C virus–associated mixed cryoglobulinemia with direct-acting antiviral agents. Hepatology 2016; 63:408–17.
51. Kondili LA, Weimer LE, Mallano A, et al. HCV-related mixed cryoglobulinemia: data from PITER, a nationwide Italian HCV cohort study. J Hepatol 2016;64:S618.
52. De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum 2012;64: 843–53.
53. Sneller MC, Hu Z, Langford CA. A randomized controlled trial of rituximab following failure of antiviral therapy for hepatitis C virus-associated cryoglobulinemic vasculitis. Arthritis Rheum 2012;64:835–42.
54. Saadoun D, Resche Rigon M, Sene D, et al. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. Blood 2010;116:326–34 [quiz: 504–5].
55. Dammacco F, Tucci FA, Lauletta G, et al. Pegylated interferon-alpha, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. Blood 2010;116:343–53.
56. Sène D, Ghillani-Dalbin P, Amoura Z, et al. Rituximab may form a complex with IgMkappa mixed cryoglobulin and induce severe systemic reactions in patients with hepatitis C virus-induced vasculitis. Arthritis Rheum 2009;60:3848–55.
57. Dammacco F, Sansonno D, Han JH, et al. Natural interferon-alpha versus its combination with 6-methyl-prednisolone in the therapy of type II mixed cryoglobulinemia: a long-term, randomized, controlled study. Blood 1994;84:3336–43.
58. Hausfater P, Cacoub P, Assogba U, et al. Plasma exchange and interferon-alpha pharmacokinetics in patients with hepatitis C virus-associated systemic vasculitis. Nephron 2002;91:627–30.
59. Younossi ZM, Stepanova M, Marcellin P, et al. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: results from the ION-1, -2, and -3 clinical trials. Hepatology 2015;61:1798–808.
60. Byrnes V, Miller A, Lowry D, et al. Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition. J Hepatol 2012;56:549–56.